IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR.	ATTORNEY DOCKET NO.
10/736,084	12/15/2003	Joseph C. Walsh	2003P88074US

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REMARKS

Applicant hereby authorizes the PTO to charge any and all necessary fees due, or provide reimbursements of excessive fees paid, to deposit account No. 19-2179.

Entry of this Amendment is respectfully requested. No new matter is added by the Amendment.

Claims 1-32 are pending in this application; with Claims 33 and 34 having been canceled in a previous response to a Restriction Requirement.

Claim Rejections- 35 USC § 112

Applicants note with appreciation the Examiner's withdrawal of the rejection of Claims 10 and 11 under 35 U.S.C. 112, first paragraph, as being enabled; and also the Examiner's withdrawal of the rejection of Claims 1-28 as being indefinite in view of the Applicant's response dated September 15, 2006.

Claim Rejections- 35 USC § 103

Applicants also note with appreciation the Examiner's withdrawal of the rejection of Claims 21-32 under 35 U.S.C. 103(a) as being unpatentable over Acevedo et al (US 6,060,592).

On page 3 of the Office Action, the Examiner rejected Claims 1-32 under 35 U.S.C. 103(a) as being unpatentable over Fox et al (The Journal of Organic Chemistry, 1968, 33(4), 1592-99) in combination with Miller et al (J. Org. Chem. 1963, 28, 936-41).

The Examiner cites the factual inquiries under *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a):

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Rejection of Compounds of Claim 21 and Claim 30:

On page 4 of the Office Action, the Examiner rejected Claim 21 and Claim 30 as being obvious, alleging:

> "Fox et al teach the preparation of compound 8, a thymidine derivative (page 1593, Figure 2). This compound is structurally the same as the compounds in instant claims 21 and 30 except that the 5' hydroxyl group is protected in the instant compound." (Emphasis added)

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Applicants respectfully note that the application of the obviousness factors outlined in Graham v. John Deere Co. is an important test that is applicable to a broad range of different inventions and technologies, and in Graham, these obviousness factors were specifically addressed with respect to a clamp for a shank plow for plowing dirt. On the other hand, the present application relates to the synthesis of compounds containing radioactive isotopes for use in positron emission tomography (PET) for diagnostic imaging techniques.

Applicants respectfully note that the standard for obviousness in ascertaining the differences between the prior art and the claimed invention is significantly different when applied to chemical compounds and their use in chemical synthesis and as biologically active agents than the standards that are employed for mechanical inventions, such as a clamp on a plow for plowing dirt.

"For a chemical compound, a prima facie case of obviousness requires 'structural similarity between claimed and prior art subject matter ... where the prior art gives reason or motivation to make the claimed compositions.'" *In re Dillon,* 919 F.2d 688, 692 (Fed. Cir. 1990) *(en banc).* "Because of the unpredictable nature of chemical reactions, a newly-synthesized compound may be very similar in structure to known and existing compounds and yet exhibit very different properties. Further, many such new compounds are obvious in the sense that any competent chemist could have synthesized them *if requested or motivated to do so."* 2 Donald S. Chisum, Chisum on Patents §5.04[6] at 5-429 (2000) (emphasis added).

To show obviousness, the reason or motivation offered by the prior art need not offer "absolute predictability" of the results, but it requires at least a "reasonable expectation of success." *Yamanouchi,* 231 F.3d at 1343, quoting *In re Longi,* 759 F.2d 887, 896 (Fed. Cir. 1985); accord, *In re Vaeck,* 947 F.2d 488, 495 (Fed. Cir. 1991) (reversing PTO rejection of claims as obvious where prior art offered no "reasonable expectation of success"), citing *In re O'Farrell,* 853 F.2d 894, 903-04 (Fed. Cir. 1988). If the prior art makes a particular experiment or modification only "obvious to try," that does not support a finding of obviousness. See *In re Eli Lilly and Co.,* 902 F.2d 943, 945 (Fed. Cir. 1990), citing *In re O'Farrell,* 853 F.2d at 903.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one or ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), cited in MPEP 2142.

The unpredictable nature of the chemical reactions and the resulting compounds prepared from these reactions is particularly pronounced where the compounds prepared are used in medicinal applications, as is presently taught in the present

application. In particular, it has been well established that biological activities associated with compounds of different molecular structure, even if slightly different, may result in significantly different and unpredictable biological effects.

The bicyclic compound 8 taught by Fox et al is an intermediate containing a 5' hydroxyl derivative of thymidine that was prepared by the hydrolysis of compound 4. See figure 2, page 1593. In addition, as an intermediate that is useful for the preparation of other biological active compounds, such as compound 6 as noted by the Examiner, Fox et al teach that according to the reaction process, compound 8 must be formed as the free 5' hydroxyl derivative of thymidine under the hydrolysis condition such that the process for the reaction of compound 8 with liquid ammonia forms the desired compound 6. Fox et al further teach that various derivatives of the tricylic compound 6 may then be prepared from compound 8. Accordingly, Fox et al teach that the preparation of compounds of biological interest such as compound 6 may be prepared by using intermediate compounds such as 8, and the intermediate compound 8 with the 5' unprotected hydroxyl derivative are prepared and further employed to synthesize the tricyclic compound 6.

Fox et al do not teach nor suggest the method, the purpose nor the motivation for adding a hydroxyl protecting group to the 5' hydroxyl group of compound 8 to form the compound as recited in Claim 21 and 30, as such an extra step in the process are not useful, feasible nor efficient for the formation of the tricyclic compound 6.

Accordingly, one skilled in the art examining the disclosure of Fox et al would have been motivated to simply use the free 5' hydroxyl compound 8 to prepare various biologically active compounds such as the tricyclic compound 6, and would not have been motivated to prepare a derivative of compound 8 to form the 5' hydroxyl protected compounds recited in Claim 21 and Claim 30. That is, the intermediate compounds taught by Fox et al are different, the process is different and the resulting products formed form this process is different from the compounds recited in Claim 21 and Claim 30.

The Examiner also rejected the trityl enolate compound recited in Claim 29, citing Miller et al who disclose a thymidine derivative II (page 936, Figure 1) as being "structurally very close" to the compound claimed in Claim 29, "except that the carbonyl group in the base is not present as an enolate," and the Examiner comments that "such an enolate structure is an important intermediate taught by Fox (above)." The Examiner further note that

> "Fox teaches the conversion of the anhydro intermediate 4 to the derivative 5, which is the same as the compound obtained in step (c) of instant claim 1. A derivative that structurally similar to the compound in step (a) of claim 1 (the protected derivative) is taught by Miller (structure III of Miller in Figure 1). Even though the structure of the anhydro derivatives are slightly different in both Fox and Miller one of ordinary skill in the art will recognize that the sequence of steps can be applied to make the compound in instant claim 1 via the steps as instantly claimed with slight modifications. Such a modification based on the prior art is well within the purview of one of ordinary skill in the art.

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Based on the teachings of the prior art, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make compounds as claimed in instant claims 21-30 via the process as claimed in instant claims 1-20 since structurally very close compounds as instantly claimed and steps for the same are seen to be taught in the prior art." (Emphasis added)

Applicants respectfully traverse the Examiner's characterization of the cited art references as applied to Applicant's invention.

As noted by Fox et al (JOC, page 1593, Figure 2), the intentional preparation of an enolate of the thymidine base such as compound 3 invariably result in the cyclization to form the tricyclic structures as represented by compound 4, compound 6 and compound 7. That is, Fox et al teach the formation of a compound that is substituted with a 3' O-L group (see compound 3, 4 and 8, figure 2), where L is a leaving group such as a Ms group, will invariably undergo cyclization to form a tricyclic compound when an intermediate enolate is prepared on the thymidine base.

On the other hand, the compound recited in Claim 29 comprises a 3' O-L that is an Ms leaving group and a methyl ether enolate in the thymidine base, but the compound that is formed is stable and does not undergo cyclization to form a tricyclic structure as taught by Fox et al. That is, one skilled in the art viewing compound II (page 936, Figure 1) of Miller et al and the teaching of Fox et al for the formation of enolate ethers could not start with the compound II of Miller et al and prepare the enolate compound of Claim 29 using the method of Fox et al without forming the "undesired" tricyclic compounds suggested by Fox et al. In addition, neither Fox et al alone or Fox et al in combination with Miller et al, teach, suggest or provide any motivation to prepare the compound recited in Claim 29, and any such combination of the use of the compounds of Miller et al with the process disclosed by Fox et al would not have any expectation of success in the preparation of the compound of Claim 29.

In addition, in contrast to the Examiner's statement that "Fox teaches the conversion of the anhydro intermediate 4 to the derivative 5, which is the same as the compound obtained in step (c) of instant claim 1," the conversion of intermediate 4 to derivative 5 (Figure 2, page 1593) is not the same nor even similar to the compound of step (c) in Claim 1 of the present application, for the following important reasons. First, compound 4 of Fox is a tricyclic derivative, while the compounds in step (b) and step (c) are bicyclic derivatives. Second, Fox et al teach the use of a tricyclic ether derivative 4 (i.e. oxygen contain compound) as the starting material, but the reaction forms the intermediate compound 5 that is a nitrogen containing compound (by replacement of the oxygen with nitrogen using ammonia). Applicants note that in Claim 1 of the present application, no such conversion of an oxygen atom to a nitrogen atom is claimed; nor does step (b) or step (c) in Claim 1 of the present application forms a tricyclic compound as taught by Fox et al.

As noted above, because of the unpredictable nature of the chemical reactions and the resulting compounds and intermediates prepared from these reactions is particularly pronounced, the Examiner's observation that the thymidine derivative II

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(page 936, Figure 1) as being "structurally similar," or "structurally very close" to the compound claimed in Claim 29; and that the structure of Claim 1 in the present application is "slightly different" are not the appropriate standards for establishing a *prima facie* case of obviousness. In addition, the Examiner cited the process of Fox et al for the conversion of compound 4 to compound 5, suggesting that the process is "the same as the compound obtained in step (c) of instant claim 1." However, as detailed above, the process taught by Fox et al is significantly distinct from the process of Claim 1 of the present application, because the intermediates are different, the process step and reagents used are different, and the resulting products taught by Fox et al is also different than those recited in Claim 1 of the present application.

Finally, in addition to the different compounds taught by Fox et al and by Miller et al, neither Fox et al nor Miller et al teach nor suggest the process recited in Claim 1 of the present application.

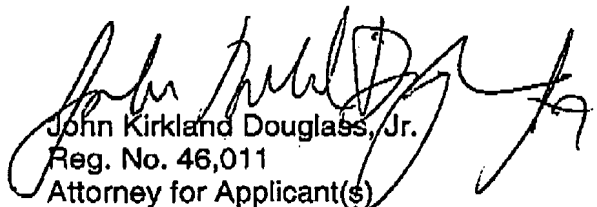
Applicants respectfully request the withdrawal of the 35 U.S.C. 103(a) rejection of Claim 1-32.

Applicants respectfully assert that Claims 1-32 are novel, and allowance of these claims is respectfully solicited. The present application is believed to be in prima facie condition for allowance, and an early action to that effect is respectfully solicited.

In view of the foregoing amendments and remarks, Applicant submits that all of the claims are in proper format and are patentably distinct from the prior art of record and are in condition for allowance.

The Examiner is invited to contact the undersigned at the telephone number listed below with and questions concerning this application.

Respectfully submitted,



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